1213. If a Petition for extension of time is needed, this paper is to be considered such Petition.

Claims 70, 72-79, 92-94 and 117-119 are pending in this application. Claims 70, 74, 92-94 and 115 are amended herein. Claim 70 is amended to recite that the array contains 4^R nucleic acid probes nucleic acid probes, each of which contains a double-stranded portion at the 3'-terminus and a single-stranded portion at the 5'-terminus to more distinctly claim the subject matter claimed by the applicant. Basis for the amendment can be found throughout the specification (*e.g.*, page 6, lines 10-15 and 25-29; page 21, lines 1-8 and 22-28) and the claims as filed. Claim 74 is amended by reciting fixing the array to a solid support by conjugating one strand of the double-stranded region to a coupling agent. The amendment finds basis on page 13, lines 19-24, which states that "[n]ucleic acids are bound to the solid support by covalent binding such as by conjugation with a coupling agent," and throughout the specification (*e.g.*, see page 24, lines 5-10; the claims as filed; and Figures 2, 3, 5, 7, 8, 10, 11 and 12). Claims 92-94 are amended to depend from pending claims.

Claims 117-119 are added herein. These claims find basis in the application and parent application as originally filed. For example, the subject matter of claim 117, which recites various coupling agents, finds basis throughout the specification (for example, see page 13, lines 19-24, and page 24, lines 5-10). The subject matter of new claim 118 finds basis throughout the specification and claims as filed. The subject matter of new claim 119, which is directed to an array that contains up to $4(2^R-1)$ nucleic acid probes, finds basis in the specification at page 12, lines 6-8.

Therefore, no new matter is added nor are any amendments made to change the scope of the claims. The amendments should place the claims and the application into condition for allowance. Included as an attachment is a marked-up version of the claims that are being amended, as per 37 CFR §1.121.

A terminal disclaimer is filed herewith.

AIPA

The Office Action states that the instant application was filed before November 29, 2000, and, thus, is not subject to the provisions of the AIPA. It is noted, however, that a CPA of this application was filed on April 4, 2001, thereby bringing this application under the provisions of the AIPA.

REJECTION OF CLAIM 115 UNDER 35 U.S.C. §112, SECOND PARAGRAPH

Claim 115 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter.

It is respectfully submitted that this rejection is rendered moot with respect to claim 115, which is cancelled without prejudice.

THE REJECTION OF CLAIMS 70-74, 76-79, 89, 91-94, and 114-116 UNDER 35 U.S.C. §102(e)

Claims 70-74, 76-79, 89, 91-94, and 114-116 are rejected under 35 U.S.C. § 102(e) as anticipated by Deugau *et al.* (U.S. Patent 5,508,169) because Deugau *et al.* allegedly discloses an array of probes where each probe has a double-stranded portion and a single-stranded portion and a random nucleotide sequence of length R within the single-stranded portion; an array that includes about 4^R different nucleic acid probes; and solid supports containing such arrays. This rejection is respectfully traversed.

RELEVANT LAW

Anticipation requires the disclosure in a single prior art reference of each element of the claim under consideration. In re Spada, 15 USPQ2d 1655 (Fed. Cir, 1990), In re Bond, 15 USPQ 1566 (Fed. Cir. 1990), Soundscriber Corp. v. U.S.. 360 F.2d 954, 148 USPQ 298, 301, adopted 149 USPQ 640 (Ct. Cl.) 1966. See, also, Richardson v. Suzuki Motor Co., 868 F.2d 1226, 1236, 9 USPQ2d 1913, 1920 (Fed. Cir.), cert. denied, 110 S.Ct. 154 (1989). "[A]ll limitations in the claims must be found in the reference, since the claims measure the invention". In re Lang, 644 F.2d 856, 862, 209 USPQ 288, 293

(CCPA 1981). Moreover it is incumbent on Examiner to identify wherein each and every facet of the claimed invention is disclosed in the reference. Lindemann Maschinen-fabrik Gmbh v. American Hoist and Derrick Co., 730 F.2d 1452, 221 USPQ 481 (Fed. Cir. 1984). Further, the reference must describe the invention as claimed sufficiently to have placed a person of ordinary skill in the art in possession of the invention. An inherent property has to flow naturally from what is taught in a reference In re Oelrich, 666 F.2d 578, 581, 212 USPQ 323, 326 (CCPA 1981).

THE CLAIMS

Independent claim 70 and its dependent claims 71-73 and 77-79 are directed to an array of nucleic acid probes, where each probe has a double-stranded portion at the 3'-terminus, a single-stranded portion at the 5'-terminus, and a random nucleotide sequence of length R within the single-stranded portion.

Independent claim 74 and its dependent claims 75, 76, 90-94, 115, and 117-118 are directed to an array of nucleic acid probes, wherein each probe comprises a single-stranded portion at one terminus and a double-stranded portion at the opposite terminus, where the single-stranded portion includes a random nucleotide sequence of length R, and one strand of the double-stranded portion is conjugated to a coupling agent through which the probes are fixed to a solid support.

Independent claim 119 is directed to an array comprising up to $4(2^R-1)$ nucleic acid probes, where each probe comprises a random nucleotide sequence of length R.

DISCLOSURE OF DEUGAU *et al.*

Deugau *et al.* discloses sets of double-stranded oligonucleotide "indexing linker molecules" that have a first protruding single strand of a unique sequence of 3, 4, or 5 nucleotides, and a second protruding single strand of any number of nucleotides on the other end of the double-stranded portion, where neither

single-stranded end, when paired to a complementary nucleotide cohesive end, will function as a restriction endonuclease recognition site. Deugau *et al.* discloses a comprehensive panel of indexing linkers containing all possible unique cohesive end nucleic acid fragments generated by restriction endonuclease treatment (col. 8, lines 25-40). Deugau *et al.* discloses that the minimum number of identifiable probes required for a comprehensive panel containing N-nucleotide protruding ends is $[N \times (N+1)] \div 2$ (where N is the number of possible ends, which is equal to $(4^R)^2$), where R is 3, 4, or 5, the number of nucleotide protruding ends (for example, when R equals 3, a comprehensive panel of Deugau *et al.* requires 2080 probes).

Deugau *et al.* does not disclose an array of probes each of which contains a double-stranded portion at the 3'-terminus and a single-stranded portion at the 5'-terminus or an array of probes each of which contains a double-stranded portion at one terminus and a single-stranded portion at the opposite terminus. Deugau *et al.* does not disclose an array where one strand of the double-stranded portion is conjugated to a coupling agent through which the probes are fixed to a solid support. Deugau *et al.* does not disclose a probe array of 4^R nucleic acid probes, nor a probe array of $4(2^R-1)$ nucleic acid probes.

Differences between the claimed subject matter and the disclosure of the cited reference

Deugau *et al.* does not disclose an array of probes where each probe has a double-stranded portion at the 3'-terminus, a single-stranded portion at the 5'-terminus, and a random nucleotide sequence of length R within the single-stranded portion. The cited reference discloses a set of indexing linkers that includes a first end having a protruding single strand containing the unique sequence and a second end having a protruding single strand of any number of nucleotides, including zero (col. 9, lines 28-42). Thus, the indexing linkers of Deugau *et al.* may have single-stranded portions on both ends. The reference does not disclose that the double-stranded portion is at the 3'-terminus and the single-stranded portion at the 5'-terminus.

When claimed subject matter is not identically disclosed in the cited reference, but requires picking and choosing from among a number of alternatives disclosed by the reference, the reference does not anticipate (In re Arkley,, Eardly, and Long, 455 F.2d 586, 172 SPq 524 (CCPA) 1972)). Under 35 U.S.C. §102, rejections are proper only when a reference clearly and unequivocally discloses the claimed compound or directs those skill in the art to the compound without any need for picking, choosing and combining various disclosures not directly related to each other by the teachings of the reference. The cited art must clearly and unequivocally direct those of skill in art to select the alternative selected by applicant. In re Le Grice, 49 CCPA 1124, 301 F.2d 9333.

Deugau *et al.* does not anticipate claim 70 because Deugau *et al.* does not disclose an array of probes where each probe has a double-stranded portion at the 3'-terminus and a single-stranded portion at the 5'-terminus. Instead, Deugau *et al.* discloses that the single-strand oligonucleotide acts as a desirable structural element, such as to prevent exonuclease cleavage (col. 8, lines 63-67) and should be of a length different from the first end single-strand oligonucleotide containing the unique sequence so as to not interfere with the specificity of the linker for its target fragment (col. 9, lines 1-3). Deugau *et al.* does not direct the reader to select from among the class disclosed only those indexing linkers that have the properties as instantly claimed. Thus, Deugau *et al.* does not disclose all elements of claim 70 "as claimed," and therefore the reference does not anticipate claim 70.

Similarly, Deugau *et al.* does not disclose an array of probes of claim 74 where each probe has a double-stranded portion at one terminus and a single-stranded portion at the opposite terminus, where one strand of the double-stranded portion of each probe is conjugated to a coupling agent through which the probes are fixed to a solid support. Deugau *et al.* does not disclose attaching the array of probes to a solid support by conjugating to a coupling

agent as instantly claimed. The reference discloses that "each member of the panel of linkers may be immobilized ... by covalent attachment of one or both strands of the double-stranded region of the linker to a suitable substrate" (col. 11, lines 20-23) and that:

> a panel of indexing linkers is attached to spatially segregated solid phase substrates which can be prepared by known procedures, such as those described by S. S. Ghosh and G. F. Musso, (1987) Nucl. Acids Res. 15: 5353-5372" (col. 10, lines 48-51).

Ghosh *et al.* describes the direct covalent attachment of single-stranded oligonucleotides to solid supports derivatized with alkyl-amino and alkyl-carboxylic functionalities to covalently link oligonucleotides directly to solid supports. Ghosh *et al.* does not describe coupling of double-stranded molecules via a coupling agent to a support. Deugau *et al.* discloses only the direct covalent attachment of one or both strands of the double-stranded portion of the nucleic acid to the support.

Because Deugau *et al.* does not disclose linking probes to the solid support where "one strand of the double-stranded portion is conjugated to a coupling agent through which the probes are fixed to a solid support", it does not disclose all elements of claim 74, and therefore does not anticipate claim 74.

Finally, Deugau *et al.* does not anticipate claim 119 because Deugau *et al.* does not disclose an array containing up to $4(2^R-1)$ nucleic acid probes, where each probe comprises a random nucleotide sequence of length R. Deugau *et al.* discloses that a comprehensive panel of indexing linkers provides a means for attaching specific functional modifications to selected subsets of a complex mixture of nucleic acid fragments, and discloses a lower limit for the required number of probes in the comprehensive panel having a protruding single-stranded region of length R (col. 8, lines 35-40). Deugau *et al.* discloses that the number of identifiable classes is $[N \times (N+1)] \div 2$ (where N is the number of possible ends or $(4^R)^2$) or 2080 probes where there are two trinucleotide

protruding ends (where R = 3; 32,896 where R = 4, and 524,800 where R = 5). Thus, Deugau *et al.* discloses that a comprehensive panel of indexing linkers contains at least $[(4^R)^2 \times ((4^R)^2) + 1)] \div 2$ indexing linkers, where R is the number of nucleotides protruding from one end of a fragment produced by restriction endonuclease treatment. Deugau *et al.* does not disclose a degenerative array of probes. Therefore, Deugau *et al.* does not disclose all elements of claim 119, which is a directed to an array that contains up to $4(2^R\text{-}1)$ probes, "as claimed."

Thus, Deugau *et al.* does not disclose all the elements of claims 70, 74, and 119, and their dependent claims. Therefore, since Deugau *et al.* does not disclose all elements as claimed in any of the pending claims, Deugau *et al.* does not anticipate any of the pending claims.

REJECTION OF CLAIMS 75 AND 90 UNDER 35 U.S.C. §103(a)

Claims 75 and 90 are rejected under 35 U.S.C. § 103(a) as unpatentable over Deugau *et al.* (U.S. Patent 5,508,169) in view of Ghosh *et al.* (Nucleic Acid Research 15: 5353-5372 (1987)) because Deugau *et al.* allegedly teaches or suggests every element of the claimed subject matter except the specific material from which the solid support is made, and the Examiner asserts that Ghosh *et al.* cures this defect. This rejection is respectfully traversed.

RELEVANT LAW

In order to set forth a *prima facie* case of obviousness under 35 U.S.C. §103: (1) there must be some teaching, suggestion or incentive supporting the combination of cited references to produce the claimed invention (ACS Hospital Systems, Inc. v. Montefiore Hospital, 732 F.2d 1572, 1577, 221 USPQ 329, 933 (Fed. Cir. 1984)) and (2) the combination of the cited references must actually teach or suggest the claimed invention. Further, that which is within the capabilities of one skilled in the art is not synonymous with that which is obvious. Ex parte Gerlach, 212 USPQ 471 (Bd. APP. 1980). Obviousness is tested by "what the combined teachings of the references would have suggested to those of ordinary skill in the art." In re Keller, 642 F.2d 413, 425,

208 USPQ 871, 881 (CCPA 1981), but it cannot be established by combining the teachings of the prior art to produce the claimed subject matter, absent some teaching or suggestion supporting the combination (ACS Hosp. Systems, Inc. v Montefiore Hosp. 732 F.2d 1572, 1577. 221 USPQ 329, 933 (Fed. Cir. 1984)). "To imbue one of ordinary skill in the art with knowledge of the invention in suit, when no prior art reference or references of record convey or suggest that knowledge, is to fall victim to the insidious effect of a hindsight syndrome wherein that which only the inventor taught is used against its teacher" W.L. Gore & Associates, Inc. v. Garlock Inc., 721 F.2d 1540, 1553, 220 USPQ 303, 312-13 (Fed. Cir. 1983).

THE CLAIMS

Claim 75 depends from claim 74, which is directed to an array of nucleic acid probes, where each probe comprises a single-stranded portion at one terminus and a double-stranded portion at the opposite terminus, the single-stranded portion includes a random nucleotide sequence of length R, and one strand of the double-stranded portion is conjugated to a coupling agent through which the probes are fixed to a solid support, and claim 75 is directed to an embodiment further claiming the material from which the solid support may be selected. Claim 90 is cancelled herein without prejudice.

Differences Between the Claims and the Teachings of the Cited References

Deugau *et al.*

See related section above.

Ghosh *et al.*

Ghosh *et al.* teaches the direct covalent attachment of oligonucleotides in the 20-50 base-length range to solid supports derivatized with alkyl-amino and alkyl-carboxylic functionalities. Ghosh *et al.* teaches a number of chemical methods for the attachment of DNA to solid supports through stable covalent linkages, including carbodiimide-mediated end attachment or phosphodiester bonds (page 5354). The substrates include derivatized controlled-pore glass

(page 5355), cross-linked polystyrene (page 5356), and CPG or Sephacryl™ (page 5357). Oligo-nucleotides are covalently attached to the solid supports by conversion to phosphoramidate derivatives and then reacted with the derivatized reactive functionalities on the support surface, chosen from amino or carboxyl functionalities (page 5359-60 and 5369).

Ghosh *et al.* does not teach or suggest the linkage of double-stranded oligonucleotides to solid supports via coupling agents. The reference does not teach or suggest any other method of attaching oligo-nucleotides to a solid support other than direct covalent attachment of the nucleotide to reactive functionalities on the substrate surface. Ghosh *et al.* does not teach anything about the number of oligonucleotides on a support.

ANALYSIS

It is respectfully submitted that the Examiner has failed to set forth a case of *prima facie* obviousness for the following reasons.

The combination of teachings of Deugau *et al.* with the teachings of Ghosh *et al.* does not result in the instantly claimed array.

As discussed above in the traverse of the § 102(e) rejection, Deugau *et al.* does not teach an array of nucleic acid probes, wherein each probe has a single-stranded portion at one terminus, a random nucleotide sequence of length R within the single-stranded portion, and a double-stranded portion at the opposite terminus, wherein one strand of the double-stranded portion is conjugated to coupling agent through which the probes are fixed to a solid support, nor does Deugau *et al.* teach coupling double-stranded oligonucleotides via a single strand to the support. Ghosh *et al.* does not cure this defect because Ghosh *et al.* does not teach or suggest an array of nucleic acid probes, where one strand of the double-stranded portion of a proble is conjugated to coupling agent through which the probes are fixed to a solid support.

Ghosh *et al.* does not teach or suggest attaching each probe of the array to the solid support through a coupling agent. Ghosh *et al.* teaches the direct

covalent attachment of oligo-nucleotides to solid supports derivatized with alkyl-amino and alkyl-carboxylic functionalities.

Neither Deugau *et al.* nor Ghosh *et al.*, individually or in combination, teaches or suggests an array of nucleic acid probes, where each probe has a double-stranded portion at one terminus, a single-stranded portion at the opposite terminus, a random nucleotide sequence of length R within the single-stranded portion, and one strand of the double-stranded portion conjugated to a coupling agent through which it is fixed to a solid support.

Thus, the combination of teachings of Deugau *et al.* and Ghosh *et al.* does not result in the instantly claimed arrays. Therefore, because the combination of teachings of the references does not result in the instantly claimed subject matter, the Examiner has failed to set forth a *prima facie* case of obviousness.

REJECTION OF CLAIMS 70-73, 114, AND 115 FOR OBVIOUSNESS-TYPE DOUBLE PATENTING OVER U.S. Patent No. 6,007,987

Claims 70-73, 114, and 115 are rejected under the doctrine of obviousness-type double patenting as being unpatentable over claims 4 and 7 of U.S. Patent No. 6,007,987 (Cantor *et al.*) because it is alleged both sets of claims are drawn to an array of nucleic acid probes and differ only in the patent claims being drawn to a product by process while the instant claims are drawn to a product, and the Examiner alleges that the process does not patentably distinguish the instant array from the patent array. A terminal disclaimer with respect to U.S. Patent No. 6,007,987 is filed herewith.

REJECTION OF CLAIMS 70-79, 89-94, AND 114-116 FOR OBVIOUSNESS-TYPE DOUBLE PATENTING OVER U.S. Patent No. 5,631,134

Claims 70-79, 89-94, and 114-116 are rejected under the doctrine of obviousness-type double patenting as being unpatentable over claims 1-18 of U.S. Patent No. 5,631,134 because it is alleged that the claims of the '134 patent are directed to methods of making an array of probes, and the instant claims are drawn to an array of probes made by the method of the patent.

This rejection is respectfully traversed.

RELEVANT LAW

35 U.S.C. 121, third sentence, provides that where the Office requires restriction, the patent of either the parent or any divisional application thereof conforming to the requirement cannot be used as a reference against the other.

See MPEP 806, paragraph 3, which states:

> [w]here inventions are related as disclosed but are not distinct as claimed, restriction is never proper. Where restriction is required by the Office double patenting cannot be held, and thus, it is imperative the requirement should never be made where related inventions as claimed are not distinct.

See, also MPEP 804.01, which states:

> 35 U.S.C. 121 authorizes the Commissioner to restrict the claims in a patent application to a single invention when independent and distinct inventions are presented for examination. The third sentence of 35 U.S.C. 121 prohibits the use of a patent issuing on an application with respect to which a requirement for restriction has been made, or on an application filed as a result of such a requirement, as a reference against any divisional application, if the divisional application is filed before the issuance of the patent. The 35 U.S.C. 121 prohibition applies only where the Office has made a requirement for restriction. The prohibition does not apply where the divisional application was voluntarily filed by the applicant and not in response to an Office requirement for restriction. This apparent nullification of double patenting as a ground of rejection or invalidity in such cases imposes a heavy burden on the Office to guard against erroneous requirements for restrictions where the claims define essentially the same invention in different language and which, if acquiesced in, might result in the issuance of several patents for the same invention.

ANALYSIS

The instant application was subject to a Restriction Requirement in Paper 26, mailed February 6, 2002, which restricted the claimed subject matter to one of three restriction groups:

I: claims 1-5, 65-69, and 111-113, drawn to a method for creating arrays of probes;

II: claims 80-88, 95-110, and 117-122, drawn to a method for detecting target sequences and method for sequencing; and

III: claims 70-79, 89-94, and 114-116, drawn to arrays of probes.

An election of Group III was made and the requirement was made final.

Group I includes the following independent claim:

1. A method for creating an array of probes, comprising:
   a) synthesizing a first set of nucleic acids each comprising a constant sequence of length C at a 3′ terminus and a random sequence of length R at a 5′ terminus;
   b) synthesizing a second set of nucleic acids each comprising a sequence complementary to the constant sequence of the first nucleic acid; and
   c) hybridizing the first set of nucleic acids with the second set of nucleic acids, whereby the step of hybridizing creates the array of probes.

Group II includes the following independent claims:

80. A method for detecting a target nucleic acid in a biological sample comprising:
   a) contacting an array of probes with the sample, wherein each probe has a double-stranded portion, a single-stranded portion, and a random sequence within the single-stranded portion; and
   b) identifying hybrids, whereby the target nucleic acid is detected.

95. A method of sequencing a target nucleic acid, comprising the steps of:
   i) hybridizing the target nucleic acid to an array of nucleic acid probes; and
   ii) determining a hybridization pattern; whereby the target nucleic acid is sequenced by analyzing the hybridization pattern, wherein:
      a) the nucleic acid target is at least partly single-stranded; and
      b) each probe comprises a double-stranded portion, a single-stranded portion, and a random sequence within the single-stranded portion.

Thus, the Office has stated that the instantly claimed arrays are patently distinct from method claims to create the arrays or method claims that employ the instantly claimed arrays.

ANALYSIS

Cantor 5,631,134 is a divisional of application 08/322,526, now U.S. Patent 5,503,980, which is a continuation of application 07/972,012 (now abandoned). The instant application is derived from the same parent application (07/972,012). Application 07/972,012 was subjected to a Restriction Requirement in an Office Action mailed June 28, 1993. The Examiner in that case restricted the subject matter into four groups:

I: methods of determining a nucleotide sequence by hybridization, classified in class 435, subclass 6;
II: methods of making a probe, classified in class 435, subclass 91;
III: nucleic acid probes, classified in class 536, subclass 24.3; and
IV: methods to screen a biological sample, classified in class 435, subclass 6.

An election of Group I was made with traverse in application 07/972,012, and the requirement was made final. This restriction requirement separated the methods of array and probe creation from the arrays and probes (group III).

Thus, the Office has stated in a parent application and in the instant application that probes and arrays are patently distinct from methods claims to create the probes or arrays or method claims that employ such probes or arrays.

CONCLUSION

The Office has deemed the methods of groups I and II to be patentably distinct from the arrays of group III, which were elected in this application. MPEP 806, paragraph 3 states that if restriction of subject matter is required by the Office, double patenting cannot be held. In this instance, restriction in this application and in an application upon which the cited patent is based between claims to the arrays and claims to methods for creating the arrays and methods using the arrays has been required. Therefore, because there has been a restriction requirement separating methods of making an array of probes, and arrays of probes, obviousness-type double patenting cannot be held as between claims in U.S. Patent No. 5,631,134 and the presently pending claims.

* * *

In view of the remarks herein, reconsideration and allowance of the application are respectfully requested.

Respectfully submitted,
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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

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Michael Lough

ATTACHMENT TO THE AMENDMENT SHOWING MARKED-UP CLAIMS IN ACCORDANCE WITH (37 CFR §1.121)

IN THE CLAIMS:

Please amend claims 70, 74 and 92-94 as follows:

70. (Twice Amended) An array of 4^R nucleic acid probes, wherein each probe has a double-stranded portion at the 3'-terminus, a single-stranded portion at the 5'- terminus, and a random nucleotide sequence of length R within the single-stranded portion.

74. (Amended) [The array of claim 70, wherein the nucleic acid probes are fixed to] An array of nucleic acid probes, wherein each probe comprises a single-stranded portion at one terminus and a double-stranded portion at the opposite terminus, wherein

the single-stranded portion includes a random nucleotide sequence of length R; and

one strand of the double-stranded portion is conjugated to a coupling agent through which the probes are bound to a solid support.

92. (Amended) The array [solid support] of claim 74 [89], wherein the probes are labelled with a detectable label.

93. (Amended) The array [solid support] of claim 92, wherein the detectable label is selected from the group consisting of radioisotope, a stable isotope, an enzyme, an antibody, a fluorescent chemical, a luminescent chemical, a chromatic chemical, and a metal.

94. (Amended) The array [solid support] of claim 74 [89], wherein the nucleic acids are DNA, RNA, Protein Nucleic Acid (PNA), or a combination thereof.